AR201-13816A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
1,4-CYCLOHEXANEDIEMTHANOL
(CAS NO.: 105-08-8)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for 1,4-Cyclohexanediemthanol (CHDM; CAS NO.: 105-08-8) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use both the existing data on CHDM in conjunction with data from EPA-acceptable predictive computer models to adequately fulfill all the Screening Information Data Set (SIDS) endpoints. We believe that, in total, these data are adequate to fulfill all the requirements of the HPV program without need for the conduct of any new or additional tests. Furthermore, they follow the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999 in which participants are directed to maximize the use of existing studies and data from scientifically appropriate related chemicals in order to minimize animal testing.

1,4-Cyclohexanediemthanol is white waxy solid material that is manufactured to a high degree of purity. This CAS number represents a chemical that is a mixture of isomers in an approximate proportion of 30% *cis* and 70% *trans* form, respectively. At the present time, CHDM is utilized solely as an industrial intermediate in the production of polymers and resins used in various types of coatings and plastics.

TEST PLAN SUMMARY

CAS No. 105-08-8	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	Y	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	Y	-	-	Y	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	N	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	-	N
Toxicity to Reproduction	Y	Y	-	-	Y	-	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained from reputable textbook referenced within the Hazardous Substances Data Base (HSDB).

Boiling Point - A value for this endpoint was obtained from reputable textbook referenced within the HSDB.

Vapor Pressure - A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN (1,2).

Partition Coefficient - A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN.

Water Solubility - A value for this endpoint was obtained using a computer estimation-modeling program within EPIWIN.

Conclusion: All end points have been satisfied by utilizing data obtained from reference values located in reputable textbooks identified within the HSDB or through the utilization of data obtained from the various physical chemical data modeling programs within EPIWIN. The results of the various computer estimation models within EPIWIN have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks. No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using AOPWIN, a computer estimation modeling program within EPIWIN (1).

Stability in Water - This endpoint was filled by data from an abiotic degradation study that followed established guidelines and GLP assurances (OECD TG-111).

Biodegradation - This endpoint was filled by data from a study that assessed inherent biodegradability. The study followed established guidelines and GLP assurances (OECD TG-302B).

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model within EPIWIN.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from an OECD TG-203 study conducted under GLP assurances. The study quality was deemed to be “reliable without restrictions”.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP. The study quality was deemed to be “reliable with restrictions”.

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances. The study quality was deemed to be “reliable without restrictions”.

Conclusion: All endpoints have been satisfied with data from studies that were either well-documented or used OECD guideline methods and GLP assurances. All are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by oral exposure data from a study completed in 1965 and did not follow an established protocol. Nevertheless, there was sufficient documentation to deem the quality of the study as "reliable with restrictions". Several other previously conducted studies have also been cited showing similar results.

Repeat Dose Toxicity - This endpoint is filled by data from a 13-week oral toxicity study that followed established guidelines (OECD: TG-408) and GLP assurances. The study quality was deemed to be "reliable without restrictions".

Genetic Toxicity

Mutation - This endpoint is filled with a study that followed guidelines similar to those found in OECD test guideline 471. Although the study was conducted prior to the enactment of GLP assurances, it nevertheless was well documented. This study utilized *Salmonella typhimurium* (strains: TA 98, 100, 1535, 1537, and 1538) and *Saccharomyces cerevisiae* (strain: D4). The quality of this study was deemed to be "reliable with restrictions".

Aberration - This endpoint is filled with data from an *in vivo* study using rats that followed an established guideline (OECD: TG-475) and was conducted under GLP assurances. The quality of this study was deemed to be "reliable without restrictions".

Developmental Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established guideline (OECD: TG-421) and GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed to be "reliable without restrictions".

Reproductive Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established guideline (OECD: TG-421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed to be "reliable without restrictions".

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. Some studies were conducted under GLP assurances while others were conducted prior to its enactment. In total, these studies are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for CHDM were either obtained from reputable text references found in the HSDB or were estimated using the models within EPIWIN. These data indicate that CHDM is a solid at room temperature with a very low vapor pressure. It has a relatively low estimated octanol to water partition coefficient (K_{ow}=1.49) and accordingly is quite soluble in water (4,312 ppm).

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of available data and estimation modeling programs within EPIWIN. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that CHDM will distribute primarily to soil and water. Results of an abiotic degradation (hydrolysis) study that followed OECD test guideline

111 demonstrate CHDM is stable in water, as it was not hydrolyzed under acidic, neutral or basic conditions during a 5-day exposure. The inherent biodegradability of CHDM was assessed through a study that followed OECD test guideline 302. Results of this study demonstrated CHDM to be readily degraded by wastewater organisms and accordingly would be classified by the EPA as a low concern for persistence. Computer estimation models also indicate CHDM would be readily susceptible to attack by atmospheric hydroxyl radicals and would be expected to degrade in the atmosphere at a relatively fast rate with an estimated half-life of about 0.5 days. Its primary use as an industrial intermediate in the production of polymers and resins will result in minimal environmental releases.

The potential toxicity of CHDM to fish, Daphnia, and algae were determined through either well-conducted OECD guideline studies or studies that followed scientifically acceptable methods very similar to published guidelines. The results of all three studies demonstrate that CHDM is not overtly toxic to any of these organisms with a NOEC greater than 100 mg/L. Based on these data CHDM would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria. Due to its use as an industrial intermediate, the potential for significant exposures to aqueous environments is unlikely accept under accidental conditions.

The potential to induce toxicity in mammalian species following acute oral exposure is low. CHDM exhibited an LD_{50} value in rats of about 3,200 to 6,400 mg/kg. Data from a repeat exposure study in rats following OECD guidelines (TG-408) assed the toxicity of CHDM over a 13-week period. In this study CHDM, placed in the drinking water at levels of 4.0, 8.0, and 12.5 mg/ml, induced minimal signs of toxicity that were only manifested at the highest exposure level. Clinical signs of toxicity included changes in fecal consistency and urine color as well as decreases in food consumption and weight gains. There was no histological evidence of toxicity noted in any tissue. The NOAEL for this study was determined to be the mid-exposure level that was equivalent to about 480 mg/kg in males and 750 mg/kg in females. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity study in rats that followed OECD test guidelines (TG-421). This study was conducted simultaneously with the repeated dose study with CHDM in the drinking water at the above-mentioned levels. Based on the results of this study, it was concluded that CHDM was not teratogenic. While slight evidence of fetotoxicity was noted (decreased fetal weight and weight gains), it only was manifested at levels that induced significant maternal toxicity (i.e., 12.5 mg/ml). The NOEL for teratogenicity in this study was 1360 mg/kg (highest dose examined) while maternal toxicity and fetotoxicity were present at the highest exposure level with a NOEL dose of 854 mg/kg.

In conclusion, the summarized data indicate that this chemical should constitute a low risk to workers and the environment if accidentally spilled. Due to its only current known use as an industrial intermediate in the formation of polymers and no known direct applications in consumer products, exposure to the general public is minimized.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

1. Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.